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The relationship between extended D-dimer elevations and hereditary thrombophilia in COVID-19 patients

COVID-19 hastalarında uzamış D-dimer yüksekliği ve herediter trombofili arasındaki ilişki

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ABSTRACT

Aim: To compare the D-Dimer levels in patients with mild COVID-19 disease with and without hereditary thrombophilia.

Material and Method: Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G) and FXIII (V34L) gene mutations were examined in all patients included in the study for various reasons such as recurrent miscarriage and venous embolism. Patients with any mutation were included in the hereditary thrombophilia group, while patients without mutations were included in the control group. D-dimer levels of the patients were also analyzed for the second time at least 25 days after admission. All included patients had received previously at least two doses of the BioNTech-Pfizer or CoronaVac vaccines.

Results: A total of 158 patients, 46 (29.1%) male and 112 (70.9%) female, were included in the study. The mean age of the patients included in the study was 39.08 ± 9.09 years. A total of 121 patients, 33 (27.3%) men and 88 (72.7) women, with hereditary thrombophilia were in the first group. A total of 37 patients, 13 (35.1%) male and 24 (64.9%) female, who did not have any mutations, were taken as the control group. Of the patients with hereditary thrombophilia, 47 (38.8%) had Factor V Leiden, 63 (52.1%) had MTHFR gene mutations, 32 (26.4%) had PAI-1 and 12 (9.9%) had FXIII gene mutations. When the D-dimer values of both groups were examined 20-35 days after admission to the hospital, the D-dimer level of the hereditary thrombophilia group was 667.26 ±354.11 while the D-dimer level of the control group was 369.76±173.45 (P=0.031). The D-dimer level of 23 patients in the hereditary thrombophilia group and 2 patients without thrombophilia were found to be above 1000ng/ml when they came for control.

Conclusion: It should be kept in mind that if there is prolonged or newly emerging D-dimer elevation in patients who had COVID-19 disease with mild-moderate symptoms, these patients may have hereditary thrombophilia.

Keywords: COVID-19, Herediday thrombophilia, D-dimer

ÖZ

Amaç: Bu çalışmada herediter trombofili olan ve olmayan hafif Covid-19 hastalarında D-Dimer düzeylerinin karşılaştırılması amaçlanmıştır.

Gereç ve Yöntem: Tekrarlayan düşük ve venöz emboli gibi çeşitli nedenlerle daha önce Faktör V leiden (G1691A) mutasyonu, metilen tetrahidrofolat gen mutasyonu (C677T, A1298C), PAI-1 (4G-5G) ve FXIII (V34L) gen mutasyonları bakılmış olan hastalar çalışmaya alındı. Herhangi bir mutasyonu olan hastalar kalıtsal trombofili grubuna, mutasyonu olmayan hastalar kontrol grubuna alındı. Hastaların D-dimer düzeyleri başvurudan en az 25 gün sonra bir kez daha kontrol edilmişti. Çalışmaya dahil edilen tüm hastalar daha önce BioNTech-Pfizer veya CoronaVac aşılarından en az iki doz olmuştu.

Bulgular: Çalışmaya 46 (%29,1) erkek ve 112 (%70,9) kadın olmak üzere toplam 158 hasta dahil edildi. Hastaların yaş ortalaması 39,08±9,09 idi. Herediter trombofilisi olan 33 (%27,3) erkek, 88 (72,7) kadın toplam 121 hasta birinci grup olarak alındı. Herhangi bir mutasyonu olmayan 13 (%35,1) erkek ve 24 (%64,9) kadın toplam 37 hasta ise kotrol grubu olarak alındı. Kalıtsal trombofili hastalarının 47'sinde (%38,8) Faktör V Leiden, 63'ünde (%52,1) MTHFR gen mutasyonu, 32'sinde (%26,4) PAI-1 ve 12'sinde (%9,9) FXIII gen mutasyonu vardı. Hastaneye yatıştan 20-35 gün sonra her iki grubun D-dimer değerleri incelendiğinde, herediter trombofili grubunun D-dimer düzeyi 667,26 ±354,11, kontrol grubunun D-dimer düzeyi 369,76±3; 173,45 (P=0,031) olarak bulundu. Herediter trombofili grubundaki 23 hastanın ve trombofili olmayan 2 hastanın kontrole geldiklerinde D-dimer düzeyleri 1000ng/ml'nin üzerinde bulundu.

Sonuç: Hafif-orta semptomları olan COVID-19 hastalığında uzamış veya yeni ortaya çıkan D-dimer yüksekliği varsa bu hastalarda kalıtsal trombofili olabileceği akılda tutulmalıdır.

Anahtar Kelimeler: COVID-19, hereiditer trombofili, D-dimer

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INTRODUCTION

COVID-19 disease, which is a SARS-CoV-2 virus infection, appeared in China in December 2019 and was declared a pandemic by the World Health Organization in March 2020. It may be asymptomatic, or may cause severe respiratory failure and even death (1). Since the beginning of the pandemic, SARS-CoV-2 is causing both deaths and complications, especially thrombotic events, all over the world. Although the number of confirmed cases and mortality rates vary according to countries and regions, it has led to nearly 500 million confirmed cases and over 6 million deaths by 2022 (2). While studies are continuing to predict which patient will have a severe course after signs of infection appear, patients are followed closely to predict complications.

Hereditary thrombophilia is a genetically inherited disease that can cause ischemic damage at young ages, recurrent infant loss in pregnant women, and sudden death due to acute thrombosis in the coronary or cerebral arteries. Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G), FXIII (V34L) gene mutation are common mutations and are often found as the underlying cause in patients with hereditary thrombophilia. There are very few studies on whether these mutations may cause increased prothrombotic activity in COVID-19 patients (3,4,5).

Many studies have shown that despite the prophylactic anticoagulant and antiaggregant use in COVID-19 patients, thrombotic events may occur in the venous, arterial and microvascular systems (6,7). Several studies showing complications related to hypercoagulability are based on studies in which COVID-19 disease has a severe course (8). On the other hand, it has been shown that patients with mild symptoms and who are not critically ill may still have thrombosis if they have pre-existing typical thrombotic risk factors or if they are elderly. Although venous embolisms are seen more frequently than arterial embolisms, there are studies showing that the frequency of venous thromboembolism has increased recently, especially in non-critical patients (9).

D-dimers are the protein fragments that occur as a result of the destruction of fibrin bonds that take place in the last stage of coagulation. D-dimer elevation at any given time means that the coagulation system and fibrinolytic system are active (10). Monitoring D-dimer and fibrinogen levels at the initial admission and follow-up of COVID-19 patients may be informative in terms of demonstrating coagulation-related complications (11).

The aim of this study is to compare the D-Dimer levels in patients with mild COVID-19 disease with and without hereditary thrombophilia.

MATERIAL AND METHOD

The study was carried out with the permission of Lokman Hekim University, Noninvasive Clinical Researches Ethics Committee (Date: 16.02.2021, Decision No:2021/018).All procedures were carried out in accordance with the ethical rules and the principles of the Declaration of Helsinki.

This study was carried out retrospectively by scanning the files of patients who applied to the hematology and internal diseases outpatient clinic between February 2021 and January 2022. Hemogram, C-reactive protein, D-dimer, lactate dehydrogenase (LDH), Ferritin, Homocysteine, Vitamin B12, Foliate, and fibrinogen levels of all patients included in the study were analyzed at the time of admission. The diagnosis of COVID-19 of all patients included in the study was made by taking a nasopharyngeal swab and with real-time PCR method. Age, gender, smoking history, and medical history of the patients were recorded.

Factor V Leiden (G1691A) mutation, methylene tetrahydrofolate gene mutation (C677T, A1298C), and PAI-1 (4G-5G) and FXIII (V34L) gene mutations were examined in all patients included in the study for various reasons such as recurrent miscarriage and venous embolism. Patients with any mutation were included in the hereditary thrombophilia group, while patients without mutations were included in the control group. D-dimer levels of the patients were also analyzed for the second time at least 25 days after admission. Patients under the age of 18, patients with active malignancy or a history of malignancy, patients who are pregnant, patients with systemic lupus erythematosus or similar autoimmune diseases, and patients with a negative COVID-19 PCR test at admission were excluded from the study. Low molecular weight heparin (enoxaparin 40mg/day) therapy was given to patients in both groups whose D-Dimer was above 1000 at the time of admission. Patients whose general condition deteriorated after admission to the outpatient clinic and who were hospitalized were excluded from the study. All included patients had received previously at least two doses of the BioNTech-Pfizer or CoronaVac vaccines.

Statistical Analyses

All analyzes were performed using Statistical Packace for Social Sciences 20.0 (SPSS) for Windows. Fisher's Exact test was used to analyze the demographic characteristics of the patients included in the study. Student's t-test was performed to compare the means. The difference between the groups for non-parametric values was compared with the Chi-Square test. Results are given as mean ± standard deviation. $P<0.05$ was considered statistically significant.

RESULTS

A total of 158 patients, 46 (29.1%) male and 112 (70.9%) female, were included in the study. The mean age of the patients included in the study was 39.08 ± 9.09 years. A total of 121 patients, 33 (27.3%) men and 88 (72.7) women, with hereditary thrombophilia were in the first group. A total of 37 patients, 13 (35.1%) male and 24 (64.9%) female, who did not have any mutations, were taken as the control group. Of the patients with hereditary thrombophilia, 47 (38.8%) had Factor V Leiden, 63 (52.1%) had MTHFR gene mutations, 32 (26.4%) had PAI-1 and 12 (9.9%) had FXIII gene mutations. The mean duration of symptoms in both groups was between 2-4 days. None of the patients had previous coronary artery disease or cerebrovascular accident. Totally 27 patients were excluded from the study, due to secondary malignancy (n:9), autoimmune diseases (n:4), or since they were under warfarin, heparin or low molecular weight heparin (n:14). The comparison of blood tests and demographic characteristics of the study groups at the time of admission is shown in **Table**.

Table. The comparison of blood tests and demographic characteristics of the study groups at the time of admission

Feature	Hereditary thrombophilia (n=121)	Control (n=37)	P value
Gender (M/F)	33/88	13/24	0.410
Age (years)	38.02?11.46	42.51?13.59	0.68
Smoking (+/-)	51/70	15/22	0.509
Homocysteine (μmol/L)	9.91±5.22	9.42±4.41	0.802
D-Dimer (ng/ml)	202.52±81.59	185.48±73.74	0.421
Fibrinogen (mg/dL)	204.26±83.12	200.95±57.82	0.409
WBC (10^3/mL)	7.70?2.32	6.82?1.90	0.328
Trombocyte (10^3/uL)	280?100	271±81	0.964
Vitamin B12 (pg/ml)	392?140	428?149	0.417
Folate (ng/ml)	7.94?3.58	8.84?3.01	0.395

When the D-dimer values of both groups were examined 20-35 days after admission to the hospital, the D-dimer level of the hereditary thrombophilia group was 667.26 ±354.11ng/ml while the D-dimer level of the control group was 369.76±173.45 ng/ml (P=0.031). The D-dimer level of 23 patients in the hereditary thrombophilia group and 2 patients without thrombophilia were found to be above 1000 ng/ml when they came for control. Low molecular weight heparin therapy (enoxaparin 40mg/day) was given to 12 patients from the hereditary thrombophilia group and 4 patients from the control group because D-dimer level was >1000 ng/ml until the second D-dimer level was checked. Only one patient from the hereditary tromobophilia group was hospitalized during follow-up due to coronary artery disease. Pulmonary embolism was seen in only one patient and long-term anticoagulant treatment was started. No thromboembolic complications were observed in any of the patients in the control group. In the control visits after admission to the hospital, 12 patients from the hereditary thrombophilia group and 3 patients from the control group complained of increased symptoms such as cough and shortness of breath. However, none of the patients had oxygen saturation below 91% and did not need oxygen support. In 29 patients included in the study, lupus anticoagulant was tested before and it was negative.

DISCUSSION

Thrombotic complications developed during and after COVID-19 disease continue to be a serious problem for patients and clinicians. For this reason, it is important that risky patients can be selected and followed more closely. Our study is the first to predict that the presence of hereditary thrombophilia in non-critical patients may pose a risk for thrombophilia in the subacute period in COVID-19 patients.

D-dimer levels are a good marker for demonstrating hypercoagulability in COVID-19 patients (12). The blood D-dimer level is one of the parameters used to evaluate the severity of the disease at the first admission of COVID-19 patients, and APTT and PTZ are usually found to be normal during the first admission to the hospital (13). Especially in severe COVID-19 patients, the possibility of coagulopathy increases with increasing cytokine levels. In one study, the probability of coagulopathy in severe COVID-19 patients was found to be approximately 20% (14). In a meta-analysis evaluating 1551 patients, the mean D-dimer level of the patients with moderate disease was 580 ng/ml, it was 3550 ng/ml in patients with severe disease (15). In this meta-analysis, in which a total of 54 studies were evaluated, a significant association was found between D-dimer levels and mortality. In our study, the mean D-dimer level of all patients at admission was 298.53 mg/dl. In hospitalized patients, D-dimer levels can be found to be high secondary to the onset of the thrombotic process due to hypoxia, continuous interventional procedures, or direct endothelial damage of COVID-19 (16). While a D-dimer elevation of 3 times or more at the first admission was considered risky for embolism, a 4-fold or higher D-dimer level during follow-up was found to be a good indicator for mortality in hospitalized patients (17). Similarly, if D-dimer elevation still persists after the 5th day, this may be an indicator for severe COVID-19 disease and mortality (18). In another study, higher mortality rates were found in patients with D-dimer levels above 2000 ng/ml compared to patients with D-dimer levels below 2000 ng/ml (19). The prolongation of the inflammatory process and the development of endothelial dysfunction due to cytokine storm may explain the formation of

microthrombi in critically ill patients and the secondary elevation of D-dimer levels (20). None of our patients were having severe disease and in parallel with these studies, D-dimer levels of all our patients were within normal limits at the time of admission.

In a recent study, it was shown that the PA1-1 mutation both contributes to thrombus formation and increases the secretion of proinflammatory cytokines in COVID-19 patients (3). However, there are also studies showing that the severity of COVID-19 disease worsens in patients with Factor V Leiden mutation and Factor XIII mutation (21). There are also studies with similar results regarding the MTHFR gene mutation. In fact, it has been suggested in one study that the MTHFR gene mutation may be a useful marker to show the severity of COVID-19 (22). MTHFR gene mutation may affect homocysteine metabolism, resulting in high homocysteine levels. This, in turn, may activate the angiotensin type 2 receptors, causing COVID-19 to reason more damage (24). However, in our study, there was no significant increase in homocysteine levels at the time of admission in both hereditary thrombophilia and control groups. In our study, patients with severe disease were not included in the study. However, it is useful to consider that there may be primary hereditary thrombophilia in patients with thrombotic complications such as heart attack, stroke, and deep vein thrombosis secondary to COVID-19, and further studies should be conducted to clarify this issue. Similarly, in patients with previously known homocysteine elevations, recurrent miscarriage, a history of atypical thrombosis, or a family history of hereditary thrombophilia, it may be beneficial to follow the patients more closely for thrombosis after COVID-19.

Limitations

All of the patients included in the study were vaccinated against COVID-19, at different time periods. Although studies on the vaccines continue, it should be kept in mind that prolonged D-dimer elevation in these patients may be secondary to the vaccine. In only some of the patients included, antiphospholipid antibodies were checked and this is the second limitation of the study. Since the number of patients included in the study was insufficient, a subgroup analysis could not be performed for each gene mutation. Therefore, larger prospective studies are warranted.

CONCLUSION

As a result, it should be kept in mind that if there is prolonged or newly emerging D-dimer elevation in patients who had COVID-19 disease with mild-moderate symptoms, these patients may have hereditary thrombophilia.

ETHICAL DECLARATIONS

Ethics Committee Approval: The study was carried out with the permission of Lokman Hekim University, Noninvasive Clinical Researches Ethics Committee (Date: 16.02.2021, Decision No:2021/018).

Informed Consent: Because the study was designed retrospectively, no written informed consent form was obtained from patients.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: The authors have no conflicts of interest to declare.

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